Association of intraoperative blood gas analysis with patient outcome after adult cardiac surgery

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Abstract

Background: The associations of the different blood gas parameters from different blood samples harvested at different stages during adult cardiac surgery with the postoperative outcomes are inadequately studied. Methods: Adult patients undergoing elective cardiac surgery with cardiopulmonary bypass (CPB) participated in this prospective observational study. Blood gas parameters from arterial, central venous, and jugular venous blood samples harvested simultaneously at pre-determined time points (baseline with the patient awake, post-anesthesia induction but before CPB, during CPB at 30°C, during CPB at 37°C (rewarming), and at the end of surgery) were correlated with postoperative outcomes including the length of mechanical ventilation (LMV), intensive care unit stay (LICU), hospital stay (LOH), and major organ morbidity and mortality. Results: Data from 193 patients were analyzed. Multiple parameters of different blood harvested at different stages significantly correlated with one or more outcome measures based on univariate analysis ($p < 0.05$). However, only the jugular venous blood pH and carbon dioxide tension and the central venous blood pH at the end of surgery (pHcv-end) were significantly correlated with LMV, LICU, and LOH ($p < 0.05$). A more alkaline blood correlated with more favorable outcomes. After adjusting for age, surgical time, and total intravenous volume administered, multivariate analysis showed that only pHcv-end remained independently associated with LMV and LICU ($p < 0.05$). Conclusion: More alkaline blood, especially the central venous blood at the end of surgery, is associated with more favorable outcomes after adult cardiac surgery. Trial registration ChiCTR-POC-17013942, Date of registration December 15, 2017.

Background

Open cardiac surgery is a definitive therapeutic option for certain cardiovascular lesions based on efficacy and survival data.[1, 2] The procedure, however, is associated with a high incidence of various complications, including atrial fibrillation (19%),[3] acute kidney injury (~20%),[4] cerebral injury (>50%),[5] postoperative delirium (12.5–22%),[6] ischemic stroke (1.2%),[7] myocardial infarction (4.2–5.7%),[8] and death (2.3–3.1%).[8] Multiple factors, relevant to patients,[9] surgery,[10] anesthesia,[11] and cardiopulmonary bypass (CPB),[12] have been linked to the unfavorable outcomes after cardiac surgery. Thus, the factors that can be modified perioperatively and are outcome-relevant should be identified and optimally managed.

Most parameters included in blood gas analysis, such as pH, oxygen tension (PO_2), oxygen saturation (SO_2), carbon dioxide tension (PCO_2), and even lactate, are among those factors that can be modified during surgery. Associations of different blood gas parameters such as central venous blood oxygen saturation,[13] mixed venous blood oxygen saturation,[14] central venous to arterial blood PCO_2 difference,[15] and lactate[16, 17] with patient outcomes after cardiac surgery have been shown. Compared with the pH-stat, the alpha-stat blood gas management leads to improved neuropsychologic outcomes in adult patients receiving moderate hypothermic CPB.[18, 19] However, the correlations of the different parameters included in blood gas analysis from different blood samples (arterial vs. jugular

venous vs. central venous) harvested at different stages during cardiac surgery with postoperative outcomes are inadequately studied.

We hypothesized that blood gas parameters from arterial, jugular venous, and central venous blood samples harvested at different time points during cardiac surgery have different associations with postoperative outcomes. Because the normal value of each parameter falls in a range of distribution, for example, 7.35–7.45 is regarded as the normal pH range, one of the relevant questions to ask is – is there a narrow band within the normal range that is associated with a more favorable outcome?

Methods

This was a prospective observational cohort study. The Institutional Review Board of Guizhou Provincial People's Hospital approved the study (#2014099). Verbal and written informed consents were obtained from all participants before surgery.

Patients

Patients who met the following inclusion criteria from December 20, 2017, to December 30, 2018, were recruited for this study: 1) age ≥ 18 years, 2) elective cardiac surgery, and 3) CPB requirement. We excluded patients younger than 18 years or scheduled for surgeries that were emergent, off-pump, or that required deep hypothermic circulatory arrest.

Vascular cannulation

Before anesthesia induction, the following vascular cannulations were performed under local anesthesia. A 20G catheter was inserted into a radial artery at the wrist for continuous arterial blood pressure monitoring and blood sampling. A 20-cm-long 7F triple-lumen central venous catheter was inserted into the superior vena cava through the internal jugular vein for central venous pressure monitoring and blood sampling. A 20-cm-long 16G single-lumen catheter was inserted into the right internal jugular vein retrogradely until encountering resistance, and it was then slowly retracted until the blood was aspirated for jugular venous blood sampling.[20] The position of the catheter for internal jugular venous blood sampling was confirmed by fluoroscopy.

Anesthetic care

The anesthesia team administered anxiolytics to patients at their discretion before surgery. In the operating room, patients were monitored using electrocardiography, pulse oximetry, and invasive arterial blood pressure. Following pre-oxygenation, anesthesia was induced with midazolam (0.1 mg/kg), etomidate (0.2–0.5 mg/kg) or propofol (1–2 mg/kg), and sufentanil (0.2–0.5 mcg/kg). Endotracheal intubation was facilitated by muscle relaxation using vecuronium (0.1 mg/kg). Anesthesia was maintained using sevoflurane, with intermittent boluses of sufentanil for analgesia and vecuronium for muscle relaxation. Patients were mechanically ventilated with a tidal volume of 6–8 ml/kg, a respiratory

rate of 8–12 times per minute, and an inspired oxygen fraction of ~70%. A nasopharyngeal probe was used for temperature monitoring.

Surgery and CPB

Surgery was performed through midline sternotomy. Heparin was administered to maintain an activated clotting time > 480 seconds. All patients underwent non-pulsatile CPB with a membrane oxygenator. The temperature during CPB was maintained at 30°C. Patients were rewarmed to a target nasopharyngeal temperature of 37°C before the termination of CPB. The target mean arterial pressure during CPB was 60-80 mmHg. Inotropic and vasopressor options included dobutamine, epinephrine, and norepinephrine, which were given as intravenous infusions alone or in combination as needed.

Blood gas analysis

We analyzed alpha-stat arterial, jugular venous, and central venous blood gases (GEM premier 3000, Instrumentation Laboratory, Bedford, MA, USA) using blood samples from the radial artery, internal jugular vein, and central vein, respectively. Blood samples were harvested at the following time points: 1) before anesthesia induction (pre), 2) after anesthesia induction (post), 3) during CPB with body temperature at ~30°C (30°C), 4) during CPB with the patient rewarmed to ~37°C (37°C), and 5) at the end of surgery (end).

Outcome measures

The primary outcome measures included lengths of mechanical ventilation (LMV), intensive care unit stay (LICU), and hospital stay (LOH). The secondary outcome measure was the incidence of major organ morbidity and mortality (MOMM) defined by the Society of Thoracic Surgeons.[21] MOMM is a composite measure of any of the following occurrences: 1) operative mortality defined as death from any cause; 2) stroke defined as a new-onset central nervous system deficit persisting longer than 72 hours; 3) renal failure defined as a new requirement for dialysis or an increase in serum creatinine to more than 2.0 mg/dl and doubling the most recent preoperative measurement; 4) prolonged ventilation defined as a need for mechanical ventilation longer than 24 hours; 5) deep sternal wound infection; and 6) reoperation for any reason.

Data collection

We collected patients' demographic data including age, gender, weight, New York Heart Association classification, and American Society of Anesthesiologists physical status scores. We also obtained data on comorbidities including diabetes, dyslipidemia, hypertension, stroke, and myocardial infarction. And, we collected data including preoperative ejection fraction, medications (angiotensin converting enzyme inhibitors, beta-blockers, nitroglycerin, digoxin, and diuretics), procedural details (CPB time, aortic cross-clamp time, surgical time, and type of surgery), and anesthetic details (agents and drugs used, blood products and fluid administered). The results of blood gas analysis of different types (arterial, jugular venous, and central venous blood) at different pre-determined time points were recorded. We

prospectively collected outcomes including LMV, LICU, LOH, and MOMM. All patients were followed up with, and medical records were reviewed on a daily basis until discharge.

Statistical analysis

In a multiple linear regression analysis of a dependent outcome, a sample size of 190 achieves 80% power to detect an R^2 of 0.03 attributed to 1 independent variable (i.e., a blood gas parameter) when using an F-test with a significance level (alpha) of 0.05 and adjusting for an additional 5 independent variables (covariates) with an R^2 of 0.20 (0.4). The value of $R^2 = 0.03$ is equivalent to a global Cohen's f^2 effect size of 0.03 (= $R^2/(1-R^2)$), and f^2 values of 0.02, 0.15, and 0.35 represent small, medium, and large effect sizes, respectively.

We checked continuous variables for normality of their distribution. If normally distributed, we expressed them as the mean ± SD. Otherwise, we reported medians [interquartile ranges]. Categorical variables were expressed as actual numbers and percentages.

We log-transformed three outcomes (LMV, LICU, and LOH) before the linear regression analyses. We first conducted a simple (i.e., univariate) regression analysis to look for the association of a single factor (e.g., patient demographics, blood gas parameters, and other clinical covariates) with each dependent outcome (i.e., LMV, LICU, and LOH), separately. To avoid fitting too many models, we entered only those factors found significantly associated (i.e., $p < 0.05$) with all three outcomes in the multiple linear regression analysis to identify independent risk factors. Because we aimed to assess the association of a blood gas parameter with the outcome after adjusting for important covariates, if one of the blood gas parameters was found to be statistically significant in the univariate analysis, we kept it in the multivariable model, in which we implemented a backward selection procedure to select for other risk factors, with an entry and exit significance level of 0.10. We determined the collinearity between factors by variance inflation factors (< 10). We calculated the regression coefficient (beta) and its standard error to quantify the effect sizes for the final factors that remained in the multiple regression model.

Next, we dichotomized LMV, LICU, or LOH into binary outcomes (unfavorable, for values > median; favorable, for values ≤ median). We compared patient demographics, blood gas parameters, and other clinical covariates between two groups stratified by three new binary outcomes and MOMM by univariate logistic regression analyses. As a measure of effect size, we reported the odds ratio (OR) with a 95% confidence interval (CI) for each factor.

We performed all statistical analyses using the IBM SPSS 23.0 package (Chicago, IL, USA) and the SAS software version 9.4 (Cary, NC, USA). We considered two-sided p-values lower than 0.05 as statistically significant.

Results

A total of 203 patients participated in this study. We excluded 10 patients as a result of missing arterial (n = 4) or jugular venous (n = 6) blood gas data. The demographic and clinical profiles of the study population are summarized in Table 1. The average age of the 193 patients was 48 ± 10 years, and 69 (35.8%) of them were men. All 193 patients had arterial and jugular venous blood gas data at the five pre-determined time points, with 126 patients also having complete central venous blood gas data. The median (IQR) of LMV, LICU, and LOH were 510 [360–890] minutes, 1200 [1060–1300] minutes, and 14 [11-16] days, respectively. Postoperatively, 26 (13.5%) patients developed MOMM; among these, 7 (3.6%) died during hospitalization.

The clinical factors and blood gas parameters that were found to be statistically associated with any of the primary outcomes are presented in the Supplemental Table 1. Notably, the pH of jugular venous and central venous blood samples at the end of surgery (pHjv-end and pHcv-end) and the jugular venous blood carbon dioxide tension at the end of surgery (PjvCO$_2$-end) significantly correlated with all outcome measures including LMV (p < 0.001), LICU (p < 0.001), and LOH (p < 0.05). As shown in the 3D plot that depicts the associations among pHjv-end, pHcv-end, and different outcome measures (Figure 1), a higher pH or more alkaline jugular and central venous blood, was associated with more favorable outcomes (i.e., a shorter LMV, LICU, and LOH).

The clinical covariates that significantly correlated with all primary outcomes (LMV, LICU, and LOH) in the univariate analysis included age, CPB time, surgical time, fresh frozen plasma, and total input volume. Given that CPB and surgical time were highly correlated with each other (r = 0.79, p < 0.0001), we only included surgical time in the multiple regression analysis based on the consideration of collinearity. In addition, since fresh frozen plasma was only given to 23 (11.9%) patients, we dropped it from the multiple variable model. The results of the final multiple regression models are shown in the Supplemental Table 2. After adjusting for age, surgical time, and total input volume, pHcv-end was significantly associated with LMV (beta (S.E.) = −0.856 (0.408), p = 0.038) and LICU (beta (S.E.) = −0.787 (0.267), p = 0.004), but pHjv-end and PjvCO$_2$-end were no more significantly associated with the outcomes.

The factors that were found to be statistically associated with any of the four binary outcomes are presented in the Supplemental Table 3. Age was found to increase the odds of unfavorable outcomes for LMV (OR, 1.05; 95% CI, 1.01–1.08; p = 0.004), LOH (OR, 1.02; 95% CI, 1.00–1.06); p = 0.043), and MOMM (OR, 1.07; 95% CI, 1.02-1.12; p = 0.009). Among the blood gas parameters, a higher arterial blood pH at the end of surgery was found to significantly decrease the odds for unfavorable outcomes for LMV (OR, 0.94; 95% CI, 0.89–0.99; p = 0.024) and LICU (OR, 0.94; 95% CI, 0.89–0.99; p = 0.019). Statistically significant associations with LMV and LICU were also found for blood gas parameters of pHjv-end, pHcv-end, and PjvCO$_2$-end. In addition, pHcv-end was significantly associated with MOMM (OR, 0.92; 95% CI, 0.84–1.00; p = 0.041).

Discussion

Our study demonstrated the close relationship between blood gas parameters from different blood samples and postoperative outcomes depend on the harvesting time points during cardiac surgery. The pH value of the central venous blood at the end of surgery has a consistent association with different outcomes measured in this study. More alkaline blood is associated with more favorable outcomes, suggesting that there may be an optimal band within the normal range of blood gas analysis that is associated with more favorable outcomes after adult cardiac surgery with CPB.

The correlations between pH and outcomes have been investigated in patients undergoing cardiac surgery: In elderly cardiac surgical patients ($\geq$ 75 years old), the arterial blood pH measured after surgery and on admission to the ICU was significantly higher in patients without complications and in survivors (7.43 and 7.42, respectively) than in those with postoperative complications or those who did not survive (7.41 and 7.35, respectively).[22] In adult cardiac surgical patients, randomized controlled trials have shown that alpha-stat management, the strategy of maintaining more alkaline blood during moderate hypothermia, is associated with more favorable neurologic and cognitive outcomes than the alternative pH-stat management.[18, 19, 23] The standard normal pH ranges from 7.35 to 7.45 and values outside of this range are considered abnormal. However, both our study and others[22] have shown that higher pH values within the normal range (i.e., a more alkaline blood) are associated with more favorable outcomes than lower pH values (i.e., a more acidic blood) after elective adult cardiac surgery. All this suggests the existence of a narrow optimal band within the normal pH range that is associated with more favorable outcomes.

Multiple *non-pH* blood gas parameters from different blood samples harvested at different stages of surgery also correlate with the outcomes measured in our study. Our findings are corroborated by the evidence showing that, in adult cardiac surgery, a higher arterial blood lactate concentration,[16, 17] a greater central venous to arterial blood PCO_2 difference,[15] a higher[13] or lower[24] central venous blood oxygen saturation, and a lower mixed venous blood oxygen saturation[14] all correlate with unfavorable outcomes. It is also intriguing to ask, although it cannot be determined by our study, what the optimal bands within the normal ranges are of these parameters associated with more favorable outcomes.

Our study uniquely demonstrated that, although arterial blood is normally used for blood gas analysis in clinical care, venous blood gas may have a better prognostic value after cardiac surgery. However, this should not be interpreted as a statement of exclusion of arterial blood gas analysis in clinical care because the information provided by different blood gas analyses is distinctive.[25, 26] This study also showed that central venous blood gas has a more consistent correlation with the outcomes measured in our study than does jugular venous blood gas. However, the value of jugular venous blood gas has been confirmed by the finding that its desaturation is associated with impaired postoperative cognitive test performance.[27] The cause of the different results between our study and this previous study may be due to the different outcomes that were assessed. In the clinical practice, the choice of blood sample to use for gas analysis should be based on considerations including patient population, the physiology of concern, and the outcome relevance.

Our results also suggested that the blood gas analyzed at the end of surgery has a better association with outcomes in our patient population. This finding does not indicate that blood gas analysis at earlier surgical stages is not necessary. Optimal homeostasis throughout surgery may mandate for frequent blood gas analysis at different surgical stages or whenever the clinical situation calls for it. Most blood gas parameters can be readily modified by a variety of interventions within a short period of time; therefore, blood gas may need to be checked more frequently in volatile clinical situations.

Our study has limitations. We cannot establish cause-effect relationships between the results of blood gas parameters and postoperative outcomes by this cohort study, although we suspect the association between pH and outcome is likely a cause and effect relationship based on previous randomized controlled trials comparing alpha-stat and pH-stat management.[18, 19, 23] As a result of the relatively small sample size, we were unable to adequately adjust for confounding variables in the regression analyses.

Conclusions

Multiple blood gas parameters from arterial, jugular venous, and central venous blood harvested at different time points during cardiac surgery are associated with various postoperative outcomes in adult patients. Although the pH of the central venous blood at the end of surgery consistently correlates with the outcomes measured in this study, we cannot recommend using venous blood exclusively for gas analysis and only checking the central venous blood at the ending stage of surgery. While alkaline blood within the normal range correlates with favorable outcomes, the optimal pH bands within the normal pH range of different samples during adult cardiac surgery need to be identified with further research.

Abbreviations

CPB: cardiopulmonary bypass; PO_2: blood oxygen tension; SO_2: hemoglobin oxygen saturation; PCO_2: blood carbon dioxide tension; LMV: length of mechanical ventilation; LICU: length of intensive care unit stay; LOH: length of hospital stay; MOMM: major organ morbidity and mortality; pHjv-end: the pH of jugular venous blood at the end of surgery; pHcv-end: the pH of central venous blood at the end of surgery; PjvCO2-end: the jugular venous blood carbon dioxide tension at the end of surgery

Declarations

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Availability of data and materials

Please contact the authors for data requests.

Authors' Contributions

KF designed the study, collected data, analysed results, and drafted the manuscript. SG and LJ designed the study, collected data, analysed results, and edited the manuscript. XL collected data and analysed results. DX collected data and analysed results. FD analysed results and edited the manuscript. LM analysed results, interpret the study, and edited the manuscript.

Ethics approval and consent to participate

The study was approved by the Ethical Committee for Clinical Research at Guizhou Provincial People's Hospital. Protocol number of the approval: 2014099. Consent to participate in the study was obtained from all patients.

Consent for publication

Obtained from all patients involved in this study.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Patient demographic and clinical data (n=193). Data are expressed in mean ± SD or median [interquartile range] for continuous variables and in count (n) and percentage (%) for categorical variables.

Variables	Data
Patient characteristics	
Age (year)	48 ± 10
Male (n)	69 (35.8%)
Female (n)	124 (64.2%)
Weight (kg)	55 ± 10
ASA III (n)	127 (65.8%)
ASA IV (n)	66 (34.2%)
NYHA II (n)	11 (5.7%)
NYHA III (n)	175 (90.7%)
NYHA IV (n)	7 (3.6%)
Past medical history	
Diabetes (n)	1 (0.5%)
Dyslipidemia (n)	20 (10.4%)
Hypertension (n)	1 (0.5%)
Stroke (n)	3 (1.6%)
Myocardial infarction (n)	2 (1.0%)
Preoperative ejection fraction	
≤ 30% (n)	1 (0.5%)
30-49% (n)	18 (9.3%)
≥50% (n)	174 (90.2%)
Home medications	
ACEI (n)	24 (12.4%)
β-blockers (n)	71 (36.8%)
Digoxin (n)	141 (73.1%)
Diuretics (n)	182 (94.3%)
Procedure details	
CPB time (mins)	102 [78-126]
Aortic cross-clamp time (mins)	78 [55-98]
Surgical time (mins)	210 [180-246]
Mitral valve surgery only (n)	94 (48.7%)
Aortic valve surgery only (n)	17 (8.8%)
Mitral and aortic valve surgery (n)	78 (40.4%)
CABG and valve surgery (n)	4 (2.1%)
Anesthetic drugs	
Sufentanil (n)	193 (100%)
Dexmedetomidine (n)	138 (71.5%)
Propofol (n)	19 (9.8%)
Midazolam (n)	193 (100%)
Etomidate (n)	193 (100%)
Vecuronium (n)	193(100%)
Dobutamine (n)	186 (96.4%)
Norepinephrine (n)	58 (30.1%)
Epinephrine (n)	13 (6.7%)
Intraoperative input & output	
Red blood cell (n)	25 (13%)
Fresh frozen plasma (n)	23 (11.9%)
Total input volume (ml)	2053 [1849-2347]
Postoperative course	
Length of mechanical ventilation (mins)	510 [360-890]
Length of ICU stay (mins)	1200 [1060-1300]
Length of hospital stay (days)	14 [11-16]
In-hospital mortality (n)	7 (3.6%)
Postoperative complications	
KDIGO stage 1 (n)	16 (8.3%)
KDIGO stage 2 (n)	11 (5.7%)

KDIGO stage 3 (n)	3 (1.6%)
Renal failure requiring dialysis (n)	3 (1.6%)
Pulmonary infection (n)	11 (5.7%)
Pulmonary effusion (n)	57 (29.5%)
New onset stroke (n)	5 (2.6%)
Wound infection (n)	2 (1.0%)
Reoperation (n)	6 (3.1%)
Mechanical ventilation > 24 hours (n)	5 (2.6%)
Arrhythmia requiring treatment (n)	11 (5.7%)
Myocardial infarction (n)	0 (0%)
MOMM (n)	26 (13.5%)

ASA = American Society of Anesthesiologists; NYHA = New York Heart Association; ACEI = angiotensin converting enzyme inhibitor; CPB = cardiopulmonary bypass; CABG = coronary artery bypass grafting; ICU = intensive care unit; KDIGO = Kidney Disease Improving Global Outcomes; MOMM = major organ morbidity and mortality

Figures
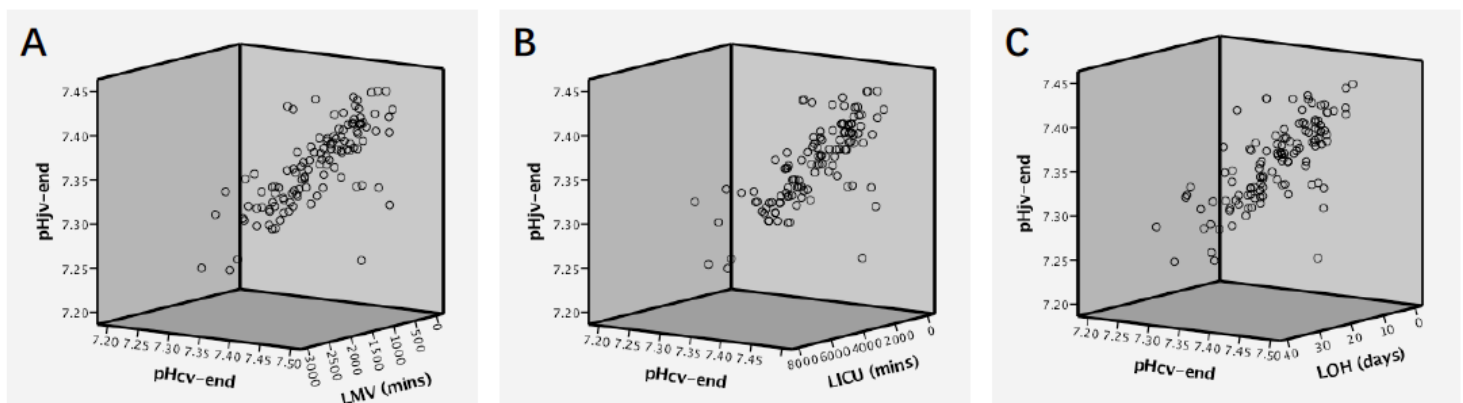
Figure 1

Correlations of the pH of jugular venous blood harvested at the end of surgery (pHjv-end) and the pH of central venous blood harvested at the end of surgery (pHcv-end) with the length of mechanical ventilation (LMV) (A), the length of stay at the intensive care unit (LICU) (B), and the length of hospital stay (LOH) (C), respectively.